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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/848,741	05/20/2004	Haitao Wu	BSA 04-02	7346

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EXAMINER	
FEDOWITZ, MATTHEW L	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/848,741	WU ET AL.	
	Examiner	Art Unit	
	Matthew L. Fedowitz	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☒ Claim(s) 26, 27 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/20/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim Objections

Claim 26 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 27 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "$-X-(CR^1R^2)_r-Z_{(2)}$." There is insufficient antecedent basis for this limitation in the claim. The limitation "$-X-(CR^1R^2)_r-Z_{(2)}$" can be interpreted as meaning 2 "Z" variables or as "-X-$(CR^1R^2)_r$-Z" of formula 2. Clarification is required to obviate the ambiguity and lack of clarity of claim 4. Claims 5-13 are also rejected because claims that ultimately depend from an indefinite claim are also indefinite. See Ex parte Cordova, 10 USPQ2d 1949 (Bd. Pat. App. & Int. 1987).

Claims 14, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps.

See MPEP § 2172.01. The omitted steps is the procedure that one practicing the invention would employ to "image a tumor" in a subject. Inclusion of the methods one would employ to "image the tumor" as set forth in claim 17 inserted into claims 14-16 would obviate the deficiencies of claims 14-16.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Frixa *et al.* (Org. Biomol. Chem., 2003, 1, 306-317). Compounds 25, 26, 45 and 46 in scheme 4 of Frixa *et al.* anticipate the compound of claims 1 and 2 represented by formula (1). As relating to claim 1, the compound of formula (1) is anticipated by compounds 25, 26, 45 and 46 as set forth in the prior art when Y^1, Y^2, Y^3, and Y^4, are in the meta position on the phenyl ring; are independently NO_2, NH_2 or carborane moieties as depicted in compounds 25, 26, 45 and 46 of scheme 4 that are linked through oxygen; where W^1, W^2, W^3, and W^4 are independent hydrophilic groups NH_2, NO_2 and where the porphyrin ring contains two hydrogen ions. As relating to claim 2, the compound of formula (1) is anticipated by compounds 25, 26, 45 and 46 as set forth in the prior art when Y^1, Y^2, Y^3, and Y^4 is $C_2HB_{10}H_{10}$ that is a *closo* meta-carborane

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

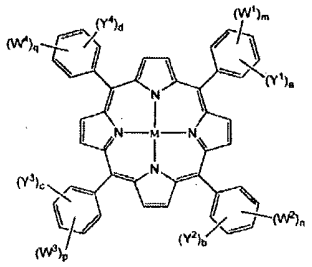
> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1) Determining the scope and contents of the prior art.
2) Ascertaining the differences between the prior art and the claims at issue.
3) Resolving the level of ordinary skill in the pertinent art.
4) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A. Claims 1-13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miura *et al.* (US 5,877,165), Dolphin *et al.* (US 4,892,941) and Frixa *et al.* (Org. Biomol. Chem., 2003, 1, 306-317).

Claim 1 is directed to a compound of the formula



(I)

wherein:

Y^1, Y^2, Y^3, and Y^4, are independently on the ortho, meta or para position on the phenyl rings, and are independently hydrogen, alkyl, cycloalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, or an alkyl, cycloalkyl, aryl, alkylaryl, arylalkyl, or heteroaryl group substituted with 1 to 4 hydrophilic groups selected from hydroxy, alkoxy, $-C(O)OR^5$, $-SOR^6$, $-SO_2R^6$, nitro, amido, ureido, carbamato, $-SR^7$, $-NR^8R^9$, or poly-alkyleneoxide; or a substituent represented by the following formula:

$$—X——(CR^1R^2)_r——Z \qquad (2)$$

provided that at least one of Y^1, Y^2, Y^3, and Y^4 represents formula (2);

X is oxygen or sulfur;

R^1, R^2, R^5, R^6, R^7, R^8, and R^9 are independently selected from hydrogen and C_1 to C_4 alkyl;

Z is a carborane cluster comprising at least two carbon atoms and at least three boron atoms, or at least one carbon atom and at least five boron atoms, within a cage structure;

r is 0 or an integer from 1 to 20;

W^1, W^2, W^3, and W^4 are hydrophilic groups independently selected from hydroxy, alkoxy, $-C(O)OR^5$, $-SOR^6$, $-SO_2R^6$, nitro, amido, ureido, carbamato, $-SR^7$, $-NR^8R^9$, or polyalkylene oxide;

a, b, c, and d independently represent an integer from 1 to 4;

m, n, p, and q are independently 0 or an integer from 1 to 4;

provided that at least one of m, n, p, and q is not zero, and each of the sums a + m, b + n, c + p, and d + q, independently represents an integer from 1 to 5; and

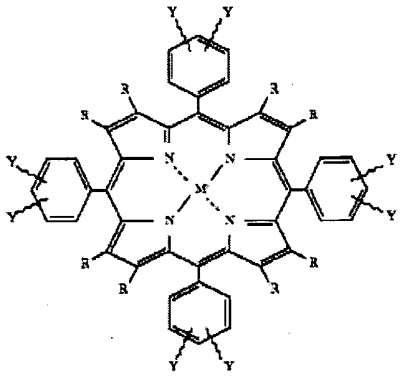
M is either two hydrogen ions; a single monovalent metal ion; two monovalent metal ions; a divalent metal ion; a trivalent metal ion; a tetravalent metal ion; a pentavalent metal ion; a hexavalent metal ion; a radioactive metal ion useful in radioisotope-mediated radiation therapy or imageable by single photon emission computed tomography (SPECT) or positron emission tomography (PET); a paramagnetic metal ion detectable by magnetic resonance imaging (MRI); a metal ion suitable for boron neutron capture therapy (BNCT) or photodynamic therapy (PDT); or a combination thereof; wherein the

porphyrin-metal complex derived from a single monovalent metal ion is charge-balanced by a counter cation, and the porphyrin-metal complex derived from a trivalent, tetravalent, pentavalent, hexavalent metal ion is charge-balanced by an appropriate number of counter anions, dianions, or trianions.

Claim 2 further limits claim 1 and is directed to a compound wherein Z is selected from the carboranes -$C_2HB_9H_{10}$ or –$C_2HB_{10}H_{10}$, wherein –$C_2HB_9H_{10}$ is nido *ortho*-, meta-, or para-carborane, and –$C_2HB_{10}H_{10}$ is *closo* ortho-, meta-, or para-carborane. Claim 3 further limits claim 1 wherein the M is vanadium, manganese, iron, ruthenium, technetium, chromium, platinum, cobalt, nickel, copper, zinc, germanium, indium, tin, yttrium, gold, barium, tungsten, or gadolinium. Claim 4 further limits claim 1 by defining a, b, c, and d as 1, and Y^1, Y^2, Y^3, and Y^4 and are represented by $-X-(CR^1R^2)_r-Z$ (2). Claim 5 further limits claim 4 by defining Z as being selected from the carboranes -$C_2HB_9H_{10}$ or –$C_2HB_{10}H_{10}$, wherein –$C_2HB_9H_{10}$ is no *ortho*-, meta-, or para-carborane, and –$C_2HB_{10}H_{10}$ is *closo* ortho-, meta-, or para-carborane. Claim 6 further

limits claim 5 to M being defined as vanadium, manganese, iron, ruthenium, technetium, chromium, platinum, cobalt, nickel, copper, zinc, germanium, indium, tin, yttrium, gold, barium, tungsten, or gadolinium. Claim 7 further limits claim 6 by defining X as O; R^1 and R^2 are H; r is 1; and m, n, p and q are each 1. Claim 8 further limits claim 7 wherein Y^1, Y^2, Y^3, and Y^4 are in the para position on the phenyl ring, and W^1, W^2, W^3, and W^4 are independently, hydroxyl or alkoxy groups. Claim 9 further limits claim 8 by defining W^1, W^2, W^3, and W^4 as alkoxy groups. Claim 10 further limits claim 9 by defining the alkoxy groups as methoxy groups. Claim 11 further limits claim to the methoxy groups being in the meta position on the phenyl ring. Claim 12 further limits claim 8 by defining W^1, W^2, W^3, and W^4 as hydroxy groups. Claim 13 further limits claim 10 by requiring the hydroxy groups to be in the meta position on the phenyl ring.

As relating to claim 1, Miura *et al.* teach boronated porphyrins according to formula 2 with the substitutions for Y, R and M as disclosed in columns 4-6 and columns 32-36. As relating to claims 2 and 5, Miura *et al.* teach the substituted positions (see column 4 lines 19-55, example 16, Claim 1, Claim 8, claims 13-15 and claim 22). As relating to claims 3 and 6, Miura *et al.*, teach the use of Cr, Mn, Fe, Co, Ni, Cu, Zn, Tc, In, Sn, Gd and Y (see column 5 lines 13-17). As relating to claim 4, Miura *et al.* teach the same compound (see columns 4-6). As relating to claims 7 -13, Miura *et al.* teach that substitutions for X and R^1 and R^2 and where r is 1 in figure I.



(2)

Miura *et al.* does not teach the substitutions for W^1, W^2, W^3, and W^4 in figure 1 where W^1, W^2, W^3, and W^4 are hydrophilic groups independently selected from hydroxy, alkoxy, -C(O)OR^5, -SOR^6, -SO2R^6, nitro, amido, ureido, carbamato, -SR^7, -NR^8R^9, or polyalkyleneoxide. Miura *et al.* also does not teach the carborane configuration of *closo* ortho-, meta- or para carborane. Nor does Miura *et al.* teach the use of Ru, Ge, Au, Ba or W; where m, n, p, and q are each 1; a compound where Y^1-Y^4 are in the para position on the phenyl ring and W^1-W^4 are independently hydroxy or alkoxy groups; a compound where W^1-W^4 are alkoxy groups; where the previously mentioned alkoxy groups are methoxy groups; where the previously mentioned alkoxy groups are in the meta position on the phenyl ring; where W^1-W^4 are hydroxy groups or where the previously mentioned hydroxy groups are in the meta position on the ring.

As relating to claim 1, Dolphin *et al.* teach a porphyrin compound with hydrophilic groups substituted on the phenyl ring (see columns 13 and 14, column 16 and claims 8-10). In addition, Bart *et al.* teach the use of polyalkylene oxide groups attached to the phenyl ring on a porphyrin structure (see formulas I and II). Frixa *et al.* teach a porphyrin compound that combines multiple carborane structures and hydrophilic groups on the phenyl ring (see compounds 25, 26, 45 and 46 in scheme 4) where m, n, p, and q are each 1. As relating to claims 2 and 5, Frixa *et al.* teach both the *nido* and *closo* carboranes and where the carborane structure

is in the ortho position with the hydrophilic groups. As relating to claim 7, the placement of the carborane and hydrophilic groups on the phenyl rings of the porphyrin structure would be obvious to one skilled in the art in order to optimize hydrophilicity of the porphyrin structure. See In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). As relating to claims 8, 11, and 13, Frixa *et al.* teach a porphyrin structure with a carborane and hydrophilic groups attached to the phenyl ring in the ortho position; as a result, altering the position on the ring would be obvious to one of ordinary skill in the art because knowing the physical and chemical properties of one of the members suggests the properties of the other members. See In re Norris, 84 USPQ 458 (CCPA 1950). As relating to claims 9, 10, and 12, Dolphin *et al.* teach a porphyrin compound with hydrophilic alkoxy groups, methoxy groups and hydroxy groups attached to the phenyl ring (see column 16 lines 10-15 and column 13 lines 35-40 respectively).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings above to obtain the compound as claimed in the instant application. All of the moieties, which are substituted in the instant application, are taught in the art, and the locations of substitution are correlative with the locations of substitution in the art. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new porphyrin compounds. See In re Payne, 203 USPQ 245 (CCPA 1979).

Frixa *et al.* provides the motivation for the carboranylporphyrins of this application by teaching that carbonyl-porphyrins rely on their anionic nature for solubility (see p 306

introduction) and that the addition of functional groups to the phenyl ring will increase the solubility of the compound (see page 312 conclusions). Moreover, Curnow et al. also provide the motivation for attempting increase the solubility of porphyrins because increased solubility allows for increased uptake into cells (see page 131 conclusions).

B. Here claims 14-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miura *et al.* (US 5,877,165), Frixa *et al.* (Org. Biomol. Chem., 2003, 1, 306-317), Dolphin *et al.* (US 4,892,941) and Foye *et al.* (Principles of Medicinal Chemistry, Fourth Edition, Williams and Wilkins 1995).

Claims 14-17 are directed to a method of imaging a tumor and surrounding tissue in a subject comprising administering to said subject a composition comprising a compound of claims 1, 11 and 13; where the imaging method is selected from magnetic resonance imaging, single photon emission computed tomography or positron emission tomography.

As relating to claims 14-17, Foye *et al.* (see pp. 904-906) teach that it is well known in the art that porphyrins can be used to image tumors. Also, It is commonly accepted that magnetic resonance imaging, single photon emission computed tomography and positron emission computed tomography are the standard for tumor imaging. Foye *et al.* do not teach compounds 1, 11 or 13; single photon emission computed tomography; positron emission tomography; or magnetic resonance imaging.

Therefore, by considering the teachings above and combining the teachings of Foye *et al.* with those set forth in Miura *et al.*, Dolphin *et al.* and Frixa *et al.*, it would have been obvious to one skilled in the art to apply the claimed compounds to a tumor imaging application as the

applicant has done with the prior art references before them. This prior art establishes that compounds of the porphyrin class are well known for use in imaging tumors due to their accumulation within tumors and make ideal candidates in methods for imaging tumors (see Foye *et al.* p. 904-906).

Foye *et al.* provides the motivation for the claimed method by phrasing the discussion in the context that further improvements in imaging can be made where porphyrins are used to for early diagnosis of tumors (see pp. 904-906).

C. Here claims 18-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miura *et al.* (US 5,877,165), Frixa *et al.* (Org. Biomol. Chem., 2003, 1, 306-317), Dolphin *et al.* (US 4,892,941) and Foye *et al.* (Principles of Medicinal Chemistry, Fourth Edition, Williams and Wilkins 1995).

Claims 18-25 are directed to a method of bimodal cancer treatment where the patient is administered compounds of claims 1, 11, or 13 and then the irradiated; where treatment also consists of irradiation, boron neutron capture theory or photo dynamic theory; and where the bimodal cancer treatment utilizes single photon emission computed tomography or positron emission tomography using a radioactive metal ion as well as magnetic resonance imaging with a paramagnetic ion to complete the bimodal treatment.

As relating to claims 18-25, Foye *et al.* (see pp. 904-906) teach the treatment of tumors using porphyrin compounds. Foye *et al.* do not teach compounds 1, 11 or 13; boron neutron capture theory; single photon emission computed tomography; positron emission tomography; or

magnetic resonance imaging. Patel *et al.* teach the use of boronated compound in the treatment of cancer (see claims 15-21).

Therefore, by considering the teachings above and combining the teachings of Foye *et al.* with those set forth in Patel *et al.*, Miura *et al.*, Dolphin *et al.* and Frixa *et al.*, it would have been obvious to one skilled in the art to apply the claimed compounds to bimodal cancer therapeutics as the applicant has done with the prior art references before them. This prior art establishes that compounds of the porphyrin class are well known for use in treating tumors due to their accumulation within the tumor itself (see Foye *et al.* p. 904-906).

Foye *et al.* provides the motivation for the claimed method by specifically stating that a primary use of porphyrin compounds is in the treatment of tumors in photodynamic therapy (see p 904 clinical applications).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew L. Fedowitz whose telephone number is (571) 272-3105 and can be reached between 9am-5:30pm (EST) M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Mr. James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew L. Fedowitz, Pharm.D., J.D.
November 15, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623